

**REMARKS**

It is our understanding that the amendments filed in response to the Final Office Action will be entered as of right upon entry of the RCE. Therefore, the present listing of the claims shows changes relative to the claims in the previously entered response.

Claims 1, 3-5, 7-13 and 15-17 are currently pending in the application. Claims 2, 6, 14 and 18 – 25 are canceled. Claims 1, 5, 9 and 13 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

**CLAIM OBJECTIONS**

Claims 18, 20, 21, 22, 23 and 24 were objected to under 37 C.F.R. 1.75, as being substantial duplicates of claims 1, 5, 7, 9, 11 and 13, respectively.

Applicant submits that claims 18-25 have been canceled, thus rendering moot the objections above. Applicant therefore respectfully requests withdrawal of the objection.

**CLAIM REJECTIONS**

**Rejection under 35 U.S.C. §112, Second paragraph.**

Claims 3 and 15 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that: “claims 3 and 15 recite ‘wherein the histograms have been subjected to kernel smoothing or kernel density estimation.’ There is insufficient antecedent basis for the histograms.”

With this Amendment, Applicant has amended independent claims 1 and 13, from which claims 3 and 15 depend, respectively, to recite the following limitation: “and wherein the information in the database comprises monospecific probe histograms.” Support for ‘wherein the information in the database comprises monospecific probe histograms’ can be found at page 4, lines 1-2, page 5, lines 21 – 22, page 6, lines 6 – 9, and page 24, lines 18 – 20, within the instant application.

As currently amended, Applicant submits that claims 3 and 15 now have proper antecedent basis. As such, Applicant respectfully requests withdrawal of the 35 U.S.C. §112 rejection and reconsideration of the claims.

**Rejection under 35 U.S.C. §103(a).**

Claims 1, 5, 9, 13, 18, 20, 22 and 24 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. No. 5,196,510 issued to Rodwell et al. (hereafter Rodwell) and further in view of “Applicant admitted prior art.” The Office Action asserts that Rodwell discloses a system allowing users to obtain information on monospecific probes in an online directory comprising:

- a web site containing a database of monospecific probe properties [computer with access to databases, col. 13, lines 48-55];
- connected to users through a computer network to allow users to enter selection criteria for retrieving monospecific probe properties [screened to find monoclonal antibodies, col. 13, lines 48-58];
- wherein the web site produces a list of matching information on monospecific probes matching the selection criteria and displays the matching information on monospecific probes on the list in an order determined by each matching probe’s similarity to the selection criteria [col. 13, lines 40-55].

The Office Action further asserts that Rodwell fails to disclose wherein said database comprises monospecific probe properties identified by flow cytometry. The Office Action states:

“Applicant’s admitted prior art discloses wherein said database comprises monospecific probe properties identified by flow cytometry.[Amendment A of 12/19/2003, Page 7]<sup>1</sup>

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Rodwell to include wherein said database comprises monospecific probe properties identified by flow cytometry as disclosed by Applicant as admitted prior art.

The ordinary skilled artisan would have been motivated to modify Rodwell per the above for the purpose of producing histograms so that diseases can be identified.”

With this amendment, Applicant has canceled claims 18, 20, 22 and 24. Furthermore, Applicant has amended independent claims 1, 5, 9 and 13 to recite the following limitation: “and

wherein the information in the database comprises monospecific probe histograms” which, as discussed above, finds support within the Specification of the instant application.

Applicant submits that Rodwell ‘510 discloses the use of “computers with access to *databases comprising the DNA and/or RNA sequences* which encode monoclonal antibodies of the IgM isotype *or of databases of amino acid sequences of such immunoglobulins.*” [col. 13, lines 51 – 54, emphasis added]. Rodwell further teaches: “[e]xamples of publicly available databases including antibody sequences include, but are not limited to the National Biomedical Research Foundation database and Intelligenetic Package...” [col. 13, lines 65 – 68]. Applicant submits that both of these databases are nucleic acid and/or protein sequence databases. In other words, Rodwell specifically teaches the use of a database whose only requirement is that it comprise sequences, DNA, RNA or amino acid, of immunoglobulins. Rodwell does not teach a database comprising monospecific probe properties *identified by flow cytometry*, nor does it teach any means of integrating such probe properties into its method. In contrast, claims 1, 5, 9, and 13 of the instant application each require that “said database comprises monospecific probe properties *identified by flow cytometry*” (emphasis added). Databases taught by Rodwell only require sequences, which are not properties that can be identified by flow cytometry.

With regard to the “admitted” prior art, the statement that “flow cytometry is well know [sic] in the art and that a property of a monospecific probe identified by flow cytometry will be evident to one of skill in the art” in no way “admits” that the use of monospecific probe properties identified by flow cytometry would be obvious, and certainly does not disclose “wherein said database comprises monospecific probe properties identified by flow cytometry”, as asserted in the Office Action. This comment merely refers to the enablement of the monospecific probe properties identified by flow cytometry but in no way teaches or suggests their combination with or substitution in the system taught by Rodwell. That is, the mere availability of monospecific probe properties identified by flow cytometry in no way teaches or suggests that these properties should be substituted for the nucleic acid or protein sequence databases taught by Rodwell. Since no teaching or suggestion to combine is provided by the cited art itself, Applicant submits that there is no motivation to combine the teachings of Rodwell et al. with enablement of monospecific probe properties identified by flow cytometry. Because

neither Rodwell et al. nor the statements made in the previous response provide any such motivation, Applicant submits that the claims are not obvious over this combination.

As such, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection of these claims.

### **Claims 3 and 15**

Dependent claims 3 and 15 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell and the alleged “applicant admitted prior art” and further in view of U.S. Pat. No. 5,596,703 issued to Eick et al (hereafter Eick). The Office Action states:

“The combination of Rodwell and applicant admitted prior art fails to disclose wherein the histograms have been subjected to kernel smoothing or kernel density estimation.

Eick discloses wherein the histograms have been subjected to kernel smoothing or kernel density estimation [col. 5, lines 44-58].

It would be obvious to one of ordinary skill in the art at the time the invention was made to modify the combination of Rodwell and applicant admitted prior art to include wherein the histograms have been subjected to kernel smoothing or kernel density estimation as taught by Eick.

The ordinary skilled artisan would have been motivated to modify the combination of Rodwell and applicant admitted prior art per the above for the purpose of smoothing the histogram”

Applicant respectfully disagrees. As noted above, Applicant submits that the statement that “flow cytometry is well known in the art and that a property of a monospecific probe identified by flow cytometry will be evident to one of skill in the art” in no way “admits” that the recited use of “monospecific probe properties identified by flow cytometry” in independent claims 1 and 13 would be obvious.

Applicant further submits that a combination of the alleged “applicant admitted prior art” with Rodwell and Eick does not provide all the elements of claims 3 and 15. As Rodwell teaches the use of amino acid or nucleic acid sequence databases, it is not clear how sequence databases, flow cytometry, kernel smoothing and kernel density estimation are to combine to reach the claimed invention.

Furthermore, even though monospecific probe properties identified by flow cytometry are enabled, there is no suggestion in the cited references to combine and/or substitute the use of

amino acid or nucleic acid sequence databases taught by Rodwell with a database comprising “monospecific probe properties identified by flow cytometry”, as required by claim 1. This lack of motivation to combine is not provided by either the alleged “applicant admitted prior art” or Eick. Therefore, regardless of whether or not Eick teaches “histograms that have been subjected to kernel smoothing or kernel density estimation”, as recited by claims 3 and 15, a combination of Rodwell, the alleged “applicant admitted prior art” and Eick is not reasonably motivated by the cited references. Applicant therefore submits that there was no motivation to combine these references, and therefore claims 3 and 15 cannot be rendered obvious by such a combination. As such, Applicant respectfully requests withdrawal of the §103(a) rejection.

#### **Claims 4 and 16**

Dependent claims 4 and 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Rodwell ‘510 as applied to claims 1, 9 and 13 above, and further in view of U.S. Pat. No. 4,870,560 issued to Kahle et al (hereafter Kahle ‘568).

The Office Action states that Rodwell ‘510 discloses the essential elements of the claimed invention except for relevance feedback, and that Kahle ‘568 discloses relevance feedback. The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Rodwell ‘510 to include relevance feedback as taught by Kahle ‘568 for the purpose of formulating a search strategy.

Applicant respectfully disagrees.

Applicant submits that claims 4 and 16 depend from claims 1 and 13, respectively. Both claims 1 and 13 have the limitation “wherein said database comprises monospecific probe properties identified by flow cytometry.” In the rejection of Claims 1, 5, 9, 13, 18, 20, 22 and 24, the Office Action states that “Rodwell fails to disclose wherein said database comprises monospecific probe properties”. Therefore, by the Office Action’s own admission, Rodwell ‘510 does not disclose all the elements of the independent claims 1 and 13. Kahle ‘568 does not provide a “database [that] comprises monospecific probe properties identified by flow cytometry”. Therefore, Applicant submits that no combination of Rodwell ‘510 and Kahle ‘568 can render the instantly claimed invention obvious.

The combination of alleged “applicant admitted prior art”, Rodwell ‘510 and Kahle ‘568 does not render the claims obvious.

Applicant submits that even a combination further including the alleged “applicant admitted prior art” does not render claims 4 and 16 obvious. As noted above, the enablement of a monospecific probe identified by flow cytometry in no way “admits” that the use of monospecific probe properties identified by flow cytometry would be obvious, nor does such enablement teach or suggest the substitution of such probe properties into the method taught by Rodwell et al. That is, there is no motivation to combine. Therefore, even if Kahle discloses relevance feedback, a combination of Rodwell ‘510 and Kahle ‘568 still lacks the “monospecific probe properties identified by flow cytometry” and is not sufficient to render claims 4 and 16 obvious. As such, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4 and 16 under 35 U.S.C. §103(a).

#### **Claims 7, 10, 21, 23, and 25**

Claims 7, 10, 21, 23, and 25 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell and the alleged “applicant admitted prior art” and further in view of U.S. Pat. No. 6,344,319 issued to Bensimon et al. (hereafter Bensimon). The Office Action states that “[t]he combination of Rodwell and applicant’s admitted prior art discloses the elements of claim 5 as noted above”, and that Bensimon discloses “wherein information in the database comprises monospecific probe histograms [Figures 1b-2c]. The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combination of Rodwell and the alleged “applicant admitted prior art” to include wherein information in the database comprises monospecific probe histograms as taught by Bensimon. Finally, the Office Action asserts that the ordinary skilled artisan would have been motivated to modify the combination per the above for the purpose of identifying abnormal allele [col. 13, lines 15-35].

Applicant respectfully disagrees. Applicant submits that claims 21, 23 and 25 are canceled. Applicant further submits that independent claim 5 has been amended to recite the limitation “and wherein the information in the database comprises monospecific probe histograms.” Applicant assumes that “claim 5”, as stated in the Office Action, is meant to

encompass all the claims from which claims 7, 10, 21, 23 and 25 depend, namely claims 5, 9 and 13.

Applicant reiterates the discussion with regard to the lack of motivation to combine the “monospecific probe properties identified by flow cytometry” with the teachings of Rodwell et al. Applicant submits that claims 7, 10, 21, 23 and 25 cannot be obvious over the combination, because no motivation is provided to combine the enablement of monospecific probe properties with Rodwell et al., together with Bensimon et al.,.

The Bensimon reference discloses methods for diagnosis of genetic diseases by molecular combing and diagnosis box and does not involve flow cytometry. Applicant submits that Figures 1b-2c of Bensimon, as cited in the Office Action, do not depict monospecific probe histograms, as is currently required for claim 5 and its dependents. Figures 1b, 1c, 2b and 2c of Bensimon are “ideal histograms of lengths of hybridized clones” [col. 13, lines 15-16; col. 13, lines 28-29, col. 13, lines 64-65; col. 14, lines 10-11]. The term “ideal histograms”, coupled with their description as “theoretical histograms” [see col. 16, lines 4] is further construed to mean that the depictions are not actual data. Moreover, Applicant submits that Figure 2a is “an illustration of the case of a clone partially overlapping the gene searched out” [col. 13, lines 37-38] and is therefore an illustration, not a monospecific probe histogram as is defined within the instant application.

In the instant application, histogram is defined as referring “to a graphical representation or plot of *data* on a single variable. *A histogram according to the invention is a plot of the fluorescence intensity of a labeled monospecific probe that binds a target on cells of a population, versus the number of cells having that intensity, for a population of cells.*” (page 8, lines 3-6, emphasis added). As the figures of Bensimon do not depict fluorescence intensity of a labeled monospecific probe, and are theoretical diagrams of lengths of clones, Applicant submits that Bensimon does not teach a histogram as defined in the specification. In light of the foregoing, Applicant submits that the combination of Rodwell, the alleged “applicant admitted prior art” and Bensimon does not provide all elements of claims 7, 10, 21, 23, and 25 and therefore does not render said claims obvious. As such, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 7, 10, 21, 23, and 25 under 35 U.S.C. §103(a).

**Claim 8**

Claim 8 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell, the alleged “applicant admitted prior art” and Bensimon and further in view of Eick. The Office Action states that the combination of Rodwell, the alleged “applicant admitted prior art” and Bensimon discloses the elements of claims 5 and 7, from which claim 8 depends, as previously noted. The Office Action further asserts that Eick discloses “wherein the histograms have been subjected to kernel smoothing or kernel density estimation [col. 5, lines 44-58]”. The Office Action concludes that the ordinary skilled artisan would have been motivated to modify the combination of Rodwell and the alleged “applicant admitted prior art” per the above for the purpose of smoothing the histogram.

Applicant respectfully disagrees. As discussed above, Applicant submits that there is no motivation to combine the enablement of monospecific probe properties identified by flow cytometry with the teachings of Rodwell, Bensimon or Eick. Furthermore, also as discussed above, Bensimon et al., and Eick et al. do not teach or suggest monospecific probe properties identified by flow cytometry, which is required by claim 5, from which claim 8 depends. As such, Applicant submits that no combination of these references can render claim 8 obvious.

Therefore, even if Eick refers to kernel density estimation, the combination is insufficient to render Claim 8 obvious.

In view of the foregoing, Applicant submits that the combination of Rodwell, the alleged “applicant admitted prior art”, Bensimon and Eick do not contain all the elements of to render claim 8 obvious. As such Applicant respectfully requests withdrawal of the §103(a) rejection of this claim.

**Claim 11**

Claim 11 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell and the alleged “applicant admitted prior art” and further in view of Eick. The Office Action states that “[t]he combination of Rodwell and applicant’s admitted prior art and Bensimon discloses the elements of claim 9 as previously noted.” The Office Action further states that Eick provides the sole deficiency not provided by the combination of Rodwell and the

alleged “applicant admitted prior art”. Finally, the Office Action states that “the ordinary skilled artisan would have been motivated to modify the combination of Rodwell and the alleged “applicant admitted prior art” per the above for the purposes of smoothing the histogram [col. 5, lines 44-58]”.

Applicant respectfully disagrees. Claim 11 is drawn to a directory computer and depends from claim 9, which was rejected under 35 U.S.C. §103(a) as being obvious over the combination of Rodwell and the alleged “applicant admitted prior art”. Applicant assumes that the mention of Bensimon as combining with Rodwell and the alleged “applicant admitted prior art” in the rejection of claim 9 was a typographical error, since it was not part of the initial statement of rejection.

As noted previously, and incorporated in its entirety herein, the combination of Rodwell and the alleged “applicant admitted prior art” does not render claim 9 obvious. Rodwell does not disclose or suggest a database comprising monospecific probe properties identified from flow cytometry. Furthermore, there is no suggestion to combine and/or substitute the use of amino acid or nucleic acid sequence databases taught by Rodwell with those comprising monospecific probe properties identified by flow cytometry. This deficiency is not provided either by the alleged “applicant admitted prior art” or by Eick.

In addition, as previously noted for claim 8, Applicant submits that figures 1b, 1c, 2b and 2c of Bensimon, which contain theoretical data that are not quantitative, and do not provide the data necessary for kernel density estimation as defined within the instant application. In addition, since figures 1b, 1c, 2b, and 2c of Bensimon are simple, readable graphs with no overlap of data or clutter. As previously noted, Eick states an important purpose of kernel density estimation is to address “*the tendency of the display to become unreadable as the amount of data it displays increases*” (col. 1, lines 39-42, emphasis added). There would have been no motivation to incorporate kernel smoothing or kernel density estimation to such simple depictions representing few, non-quantitative data points of the figures of Bensimon.

Therefore, no combination of Rodwell, the alleged “applicant admitted prior art” and Eick can render claim 11 obvious. As such, Applicant respectfully requests withdrawal of the §103(a) rejection of claim 11.

**Claim 12**

Claim 12 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell and the alleged “applicant admitted prior art” in view of U.S. Pat. No. 4,870,568 issued to Kahle et al (hereafter Kahle). The Office Action states that the combination of Rodwell and the alleged “applicant admitted prior art” discloses all the elements of claim 12 except for relevance feedback, and that Kahle discloses relevance feedback [col. 2, line 60 through col. 3, line 15]. The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combination of Rodwell and the alleged “applicant admitted prior art” to include relevance feedback as taught by Kahle. The Office Action concludes that the ordinary skilled artisan would have been motivated to modify the combination of Rodwell and the alleged “applicant admitted prior art” per the above for the purpose of formatting a search strategy [col. 2, lines 55-61].

Applicant respectfully disagrees. Applicant submits that claim 12 depends from claim 9, which was rejected under §103(a) as being unpatentable over Rodwell and the supposed “applicant admitted prior art.” As discussed above, Applicant submits that there is no motivation to combine the enablement of monospecific probe properties identified by flow cytometry with the teachings of Rodwell. Therefore, the combination of Rodwell and the alleged “applicant admitted prior art” does not render claim 9, from which claim 12 depends, obvious. Addition of Kahle to provide the relevance feedback aspect does not remedy this deficiency within claim 12. As such, Applicant respectfully requests withdrawal of the outstanding §103(a) rejection of this claim.

**Claim 17**

Claim 17 is rejected under 35 U.S.C. §103(a) as being unpatentable over Bensimon in view of Eick. The Office Action states that “Bensimon discloses comparing two monospecific probe histograms comprising the steps of analyzing a first histogram, analyzing a second histogram and comparing the analyzed histograms.” The Office Action further states that Bensimon discloses the elements of claim 17 as noted previously, except that Bensimon fails to disclose kernel smoothing or kernel density estimation. The Office Action states that Eick discloses kernel smoothing and kernel density estimation, and that it would have been obvious to

one of ordinary skill in the art at the time the invention was made to modify the combination of Rodwell and the alleged “applicant admitted prior art” to include wherein the histograms have been subjected to kernel smoothing or kernel density estimation as taught by Eick. The Office Action further states that “the ordinary skilled artisan would have been motivated to modify the combination of Rodwell and the applicant admitted prior art per the above for the purposes of smoothing the histogram [col. 5, lines 44-58].”

Applicant respectfully disagrees. Applicant assumes that inclusion of the alleged “applicant admitted prior art” within the last assertion was a clerical error, since it was not part of the initial statement of rejection.

As previously noted, the Bensimon reference discloses methods for diagnosis of genetic diseases by molecular combing and diagnosis box and does not involve flow cytometry. Applicant submits that Figures 1b-2c of Bensimon do not depict monospecific probe histograms as defined within the instant application. Figures 1b, 1c, 2b and 2c of Bensimon are “ideal histograms of lengths of hybridized clones” [col. 13, lines 15-16; col. 13, lines 28-29, col. 13, lines 64-65; col. 14, lines 10-11]. The term “ideal histograms”, coupled with their description as “theoretical histograms” [see col. 16, lines 4] is construed to mean that the depictions are not actual data. Furthermore, Applicant submits that Figure 2a is “an illustration of the case of a clone partially overlapping the gene searched out” [col. 13, lines 37-38] and is therefore an illustration, not a histogram.

In the instant application, histogram is defined as referring “to a graphical representation or plot of *data* on a single variable. ***A histogram according to the invention is a plot of the fluorescence intensity of a labeled monospecific probe that binds a target on cells of a population, versus the number of cells having that intensity, for a population of cells.***” (page 8, lines 3-6, emphasis added). As the figures of Bensimon do not depict fluorescence intensity of a labeled monospecific probe, and are “ideal” diagrams of lengths of clones, Applicant submits that Bensimon does not teach a histogram as defined in the specification.

Furthermore, Bensimon does not disclose or suggest comparing two monospecific probe histograms comprising the steps of analyzing a first histogram, analyzing a second histogram, and comparing the analyzed histograms, as asserted in the Office Action. Moreover, Applicant was unable to locate any support within Bensimon to support the statement within the Office

Action that “Bensimon discloses comparing two monospecific probe histograms comprising the steps of analyzing a first histogram, analyzing a second histogram and comparing the analyzed histograms.”

Even if the Eick reference provides for kernel smoothing and kernel density estimation, Eick does not remedy:

(1) the absence in Bensimon of a monospecific probe histogram as defined in the present invention; and,

(2) the lack of disclosure or suggestion by Bensimon of comparing two histograms.

Therefore, the combination of Eick and Bensimon does not render claim 17 of the present invention obvious. In light of the fact that Bensimon does not provide histograms as defined within the instant application, and in view of the fact that there would have been no motivation to combine the depictions of Bensimon with kernel smoothing or kernel density estimation, and further in light of the fact that the data provided by figures 1b, 1c, 2b and 2c of Bensimon do not provide sufficient data for kernel density estimation, Applicant respectfully requests withdrawal of the §103(a) rejection of claim 17.

#### **Claim 19**

Claim 19 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Rodwell and the alleged “applicant admitted prior art” and further in view of Bensimon.

Applicant submits that claim 19 has been canceled.

With this Amendment, the Applicant has made an earnest effort to respond to all issues raised in the Office Action of March 11, 2004, and to place all claims presented in condition for allowance.

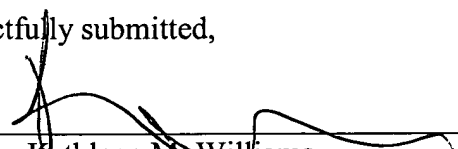
Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant’s representatives would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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Respectfully submitted,

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